# A quantitative model for bacterial growth and decline

*A model for microbial growth is proposed that includes lag, growth and decline phases. The model assumes that germination, repair or lag and the death processes are all first-order. It assumes that growth is inhibited and eventually stopped by an accumulation of toxic metabolites or depletion of a limiting substrate from cell growth and metabolism. Parameters for the model are computed by trial and error using spreadsheet software. Examples of the model fitted to select growth curves are presented. A comparison of the parameters from this model is made with those from the Gompertz equation.*

## Introduction

The ability to mathematically describe the growth of bacteria in microbiological growth media or food is essential for predicting and comparing growth characteristics. A traditional approach has been to plot the log of the bacterial population versus time, then visually estimate (subjectively) the lag phase and determine the slope of the linear portion of the growth phase.

More recently, a number of mathematical models were proposed to describe the growth of bacteria (Labuza et al. 1990). These were not based on growth processes or microbial kinetics. Zwietering et al. (1990) compared several sigmoidal functions (including logistic, Gompertz, Richards, Schnute and Stannard) which describe bacterial growth. They concluded that the Gompertz function was 'statistically sufficient and easy to use'. Changes in the parameter values from environmental factors were successfully fitted by multiple regression equations and microbial growth can be predicted for a range of conditions (Bratchell et al. 1989, Buchanan et al. 1989, Gibson et al. 1988, Gibson and Roberts 1989, Buchanan and Phillips 1990, Palumbo et al. 1991). However, the Gompertz function has several characteristics not always compatible with microbial growth (Garthright 1991). There is no period of linear exponential growth, the time of the maximum growth rate is at 37% of the growth from inoculum to stationary phase (in logarithms) and the end of the lag phase is at 6·7% of the growth. The model does not extend beyond the stationary phase.

Many researchers determined first order parameters or growth rates for the exponential phase of growth (Bailey and Ollis 1986, Cooper 1991). The effect of growth factors on the growth rate can be described by response surface equations (Thayer et al. 1987). The model of Ratkowsky et al. (1983) related temperature to the square root of the growth

rate. McMeekin et al. (1987) extended this model to include water activity.

Schoolfield et al. (1981) developed biological rate models based on the Arrhenius relationship and Broughall et al. (1983) used them for bacterial growth. Monod (1949) assumed the growth rate was dependent upon the concentration of a limiting substrate. This relationship was used by Comby et al. (1989) to model the inhibitory effect of chloramphenicol on *E. coli*. Complex, substrate-based models for bacterial growth were presented by Kono (1968), Verhoff et al. (1972) and Petrova and Stepanova (1990). However, these models are not readily applicable to bacterial growth in media or foods because the limiting growth factors and their respective concentrations are usually not known. In most foods, substrate concentrations are not the limiting factor.

The purpose of this paper is to present a model for microbial growth based on several assumptions about bacterial growth and decline which can be tested experimentally. The model does not require knowledge of substrate concentrations. Its applicability to food microbiology will be demonstrated by fitting growth data from foodborne pathogens.

*Bacterial growth model*

The postulated stages in bacterial growth and decline are illustrated schematically on Fig. 1. The transition of a bacterial cell from stage A to B represents a change from a non-growing cell, e.g. spore germination, injury repair or adjustment to a new environment, all or a combination of which may produce a lag phase. This transition is postulated to be first-order.

$$N_B = N_A e^{k_1 t} \tag{1}$$

where $t$, time; $k_1$, rate parameter ($h^{-1}$); $N_B$, number of cells in stage B; $N_A$, number of cells in stage A.

The number of active cells then increases by binary division (B to C).

$$N_C = N_B 2^{t/G} \tag{2}$$

$G$, generation time ($h$); $N_C$ number of cells in stage C.

The generation time ($G$) is not constant throughout the growth period. $G$ has an initial value (primary generation time, $k_2$, $h$) which is increased by $k_3$ (ml $cfu^{-1}$) times the accumulated sum of the cell populations (h cfu $ml^{-1}$).

$$G = k_2 + k_3 \sum_i^t N_{Ci} \tag{3}$$

$k_2$, primary generation time parameter (h); $k_3$, sum population term (ml $cfu^{-1}$).

The sum is the area under the growth curve from inoculation to $t$. The incorporation of the $k_3$-sum population term means that cell growth will be inhibited and eventually stopped as the population size increases. This is consistent with a depletion of limiting substrates or the accumulation of toxic metabolites (Bailey and Ollis 1986). As time increases, $G$ increases making $t/G$ tend toward zero and thereby leading to the stationary phase. The death of the cells

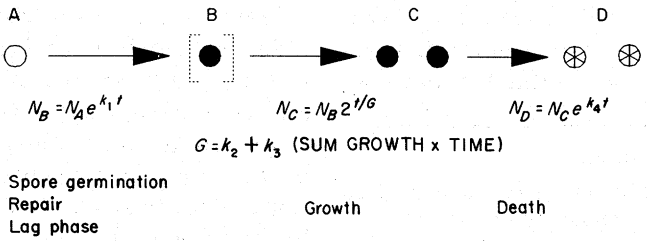


**Fig. 1**. Bacterial growth model.

(stages C to D) is assumed to be first-order ($k_4$, $h^{-1}$), i.e. a constant fraction of cells die in a given time.

$$N_D = N_C e^{k_4 t} \quad (4)$$

$k_4$, decline parameter; $N_D$, number of cells in stage D.

Viable counts at any time are the sum of the number of cells in stages A and C; stage B is a transition state and is indistinguishable from C. Assembling the model's stages gives this expression for changes in cell population $ml^{-1}$ with increasing time from $t_i$ to $t_j$.

$$N_{Cj} = [k_1 N_{Ai}(t_j - t_i) + (1 - k_4(t_j - t_i))N_{Ci}]\, 2^{((t_j - t_i)/G)} \quad (5)$$

A numerical solution to combined equations 3 and 5 were approximated by stepwise spreadsheet algorithms (Appendix). The inoculum and estimates of the four parameters were entered in the entry cells and the spreadsheet calculated values for each increasing time interval. A graph of the calculated viable count with time was superimposed upon the spreadsheet. Plate counts from a growth experiment were also displayed on the graph. New parameter estimates were then entered and the calculated curve compared to the plate counts. Additional parameter estimates were tried until a satisfactory fit was obtained. Because of the accumulated growth term, the spreadsheet used actual bacteria counts in the calculations instead of the log of the counts. Values obtained for the parameters can vary depending on the time interval chosen, 20 to 50 time intervals between inoculation and the onset of the stationary phase are recommended.

*Bacterial growth curve parameters from experimental data*

Two separate inoculations of spores of *Clostridium botulinum* 62A (FDA) were grown in BAM broths at 35°C and enumerated inside an anaerobic chamber on BAM agar plates using a Spiral Systems automated plater (Call et al.

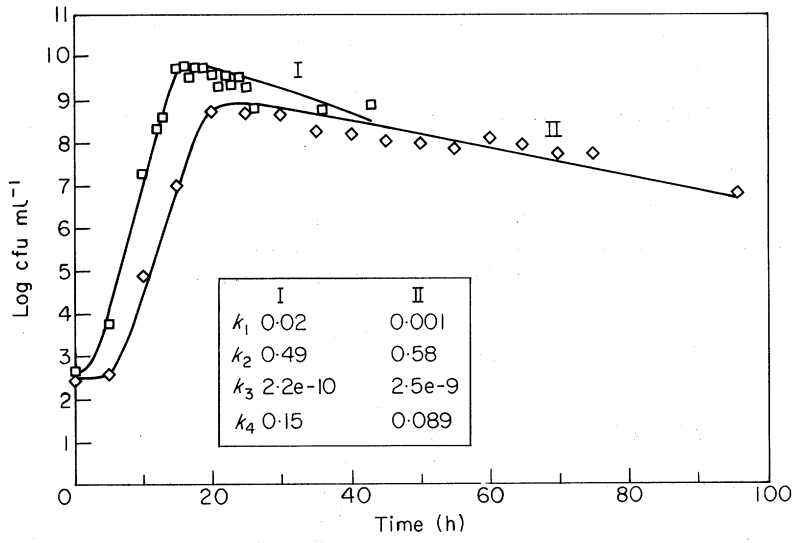


**Fig. 2.** Growth of *Clostridium botulinum* in BAM media at 35°C. □ and ◇ are populations determined by plate counts for inoculation I and II, respectively. The solid lines are the growth curves computed from the parameters.

1991). The model was able to accurately describe the growth rate data (Fig. 2). Inoculation I germinated and grew sooner and had a larger value for $k_1$ value than inoculum II. The times for the populations in inoculation I and II to double were 3 and 6 h, respectively. The values for $k_2$ were similar, but curve I had a lower value for $k_3$ due to a higher maximum population size. Declines began immediately after the maximum and were approximated by a first-order process.

The seventeen growth curves of *Listeria monocytogenes* in broth without nitrite from the data of Buchanan et al. (1989) were used. These data were measured at various temperatures, pH and NaCl levels. No plate counts were obtained after the maximum growth, therefore in this analysis, $k_4$ was fixed at 0·0 $h^{-1}$. The primary generation times determined by this model ($k_2$) and the generation times using the Gompertz function are compared (Table 1). The two generation times varied similarly over the ranges of the growth factors although this model predicted a primary generation time that averaged 16% longer than the generation time determined by the Gompertz function. This model did not calculate a traditional lag time in hours, but a half-life for the transition is given by $0{\cdot}69/k_1$. A small $k_1$ may not necessarily result in a long apparent lag time if the micro-organisms grow rapidly because nearly all of the population descends from the first cells that make the A to B transition. Values comparable to the traditional lag times may be obtained by noting the time in the spreadsheet (Appendix) that it takes

**Table 1. Comparison of $k_2$ and Gompertz derived generation times for growth of *L. monocytogenes* grown under various temperatures, pH values and NaCl levels.**

| | $k_2$ (h) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Temperature (°C) | | | | | | | | | |
| | 37 | | | 28 | | 19 | | 10 | 5 | |
| | % NaCl | | | | | | | | | |
| pH | 0·5 | 2·5 | 4·5 | 0·5 | 4·5 | 0·5 | 4·5 | 0·5 | 0·5 | 4·5 |
| 7·5 | 0·60 | 0·65 | 0·75 | 0·75 | 1·1 | 1·7 | | 5·6 | 12 | |
| 6·75 | | | | | | 1·05 | | | | |
| 6·0 | 0·55 | | | | | 1·05 | 3·05 | | 16 | 24 |
| 5·25 | | | | | | 1·15 | | | | |
| 4·5 | | | | 5·5 | | 18·0 | | | | |

| | Gompertz generation time (h) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Temperature (°C) | | | | | | | | | |
| | 37 | | | 28 | | 19 | | 10 | 5 | |
| | % NaCl | | | | | | | | | |
| pH | 0·5 | 2·5 | 4·5 | 0·5 | 4·5 | 0·5 | 4·5 | 0·5 | 0·5 | 4·5 |
| 7·5 | 0·55 | 0·49 | 0·50 | 0·58 | 0·87 | 1·12 | | 5·3 | 13·3 | |
| 6·75 | | | | | | 0·83 | | | | |
| 6·0 | 0·50 | | | | | 0·80 | 2·6 | | 13·9 | 22·4 |
| 5·25 | | | | | | 0·89 | | | | |
| 4·5 | | | | 4·4 | | 19·0 | | | | |

for the population to double initially. The initial doubling times (Table 2) were slightly smaller than the lag times determined using the Gompertz function which calculated the lag time as ending after 2·6 generations assuming 6 logs of growth (Garthright 1991). $k_3$ was nearly constant over the ranges of both factors, increasingly only at pH 4·5 or 5°C (Table 3).

Second-order equations were calculated to describe the effect of the growth factors on the constants by backwards multiple regression (RS/1, BBN Software Prod. Corp., Cambridge, MA):

$$\log k_1 = -16{\cdot}20 + 0{\cdot}1200\,(\text{temp}) + 4{\cdot}160(\text{pH}) - 0{\cdot}01291\,(\text{pH})(\text{NaCl}) - 0{\cdot}002234\,(\text{temp})^2 - 0{\cdot}3121\,(\text{pH})^2 + 0{\cdot}0112\,(\text{NaCl})^2 \quad (6)$$
$$r^2 = 0{\cdot}82$$

$$\log k_2 = 12{\cdot}677 - 0{\cdot}1092\,(\text{temp}) - 3{\cdot}4447\,(\text{pH}) + 0{\cdot}3657\,(\text{NaCl}) - 0{\cdot}04464\,(\text{temp})(\text{NaCl}) + 0{\cdot}001571\,(\text{temp})^2 + 0{\cdot}2636\,(\text{pH})^2 \quad (7)$$
$$r^2 = 0{\cdot}96$$

$$\log k_3 = 7{\cdot}43 - 4{\cdot}92\,(\text{pH}) + 0{\cdot}357\,(\text{NaCl}) - 0{\cdot}0109\,(\text{temp})(\text{NaCl}) + 0{\cdot}350\,(\text{pH})^2 \quad (8)$$
$$r^2 = 0{\cdot}84$$

*Growth / survival curve parameters*

*Listeria monocytogenes* was grown in BHI broths (28°C) having different water activities ($a_w$) from the addition of NaCl (Miller 1992). The growth slowed as the $a_w$ decreased and no growth occurred at and below $a_w$ of 0·90. To describe these data, the model was

**Table 2. Initial doubling times and Gompertz lag times for *L. monocytogenes* grown under various temperatures, pH values and NaCl levels.**

| | Initial doubling times (h) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Temperature (°C) | | | | | | | | | |
| | 37 | | | 28 | | 19 | | 10 | 5 | |
| | % NaCl | | | | | | | | | |
| pH | 0·5 | 2·5 | 4·5 | 0·5 | 4·5 | 0·5 | 4·5 | 0·5 | 0·5 | 4·5 |
| 7·5 | 2·1 | 2·9 | 3·9 | 2·0 | 4·2 | 4·6 | | 13 | 48 | |
| 6·75 | | | | | | 2·5 | | | | |
| 6·0 | 2·2 | | | | | 3·0 | 8·6 | | 47 | 78 |
| 5·25 | | | | | | 4·3 | | | | |
| 4·5 | | | | 27 | | 63 | | | | |

| | Gompertz lag time (h) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Temperature (°C) | | | | | | | | | |
| | 37 | | | 28 | | 19 | | 10 | 5 | |
| | % NaCl | | | | | | | | | |
| pH | 0·5 | 2·5 | 4·5 | 0·5 | 4·5 | 0·5 | 4·5 | 0·5 | 0·5 | 4·5 |
| 7·5 | 1·7 | 3·4 | 4·4 | 3·2 | 5·1 | 9·7 | | 15·0 | 57·7 | |
| 6·75 | | | | | | 3·9 | | | | |
| 6·0 | 2·4 | | | | | 5·7 | 10·4 | | 47·8 | 75·3 |
| 5·25 | | | | | | 7·4 | | | | |
| 4·5 | | | | 29·4 | | 68·0 | | | | |

**Table 3. Log $k_3$ values for *L. monocytogenes* grown under various temperatures, pH values and NaCl levels.**

| | Temperature (°C) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 37 | | | 28 | | 19 | | 10 | 5 | |
| | % NaCl | | | | | | | | | |
| pH | 0·5 | 2·5 | 4·5 | 0·5 | 4·5 | 0·5 | 4·5 | 0·5 | 0·5 | 4·5 |
| 7·5 | −9·7 | −9·5 | −9·7 | −10·0 | −10·0 | −9·8 | | −9·5 | −10·0 | |
| 6·75 | | | | | | −9·5 | | | | |
| 6·0 | −9·6 | | | | | −9·3 | −9·3 | | −9·3 | −7·7 |
| 5·25 | | | | | | −9·0 | | | | |
| 4·5 | | | | −7·0 | | −8·0 | | | | |

modified by assuming the first-order decline parameter ($k_4$) applied to both the inoculum and the growing cells (A and C, Fig. 1). The equation placed in spreadsheet column C (row 9 illustrated) became ((C8*(1–$D$5*(A9–A8)))–($G$5* C8*(A9–A8))). This modification permitted better fitting of $k_1$ and $k_2$ to the declining data ($a_w \leq 0{\cdot}90$) than the original model, where stage A cells must convert to B and then C before dying. In the range of $a_w$ from 0·99 to 0·93, $k_1$ decreased and $k_2$ increased; $k_3$ and $k_4$ were only slightly affected (Table 4). As $a_w$ decreased below 0·90, $k_3$ and $k_4$ increased. At these $a_w$, the importance of the numerical value and the physiological significance of the changes in $k_1$ and $k_2$ are less clear because death cell predominates. The experimental data and the fitted models are shown in (Fig. 3).

The generation times for the $a_w$ values that permitted growth were determined with this model, manual plotting and the Gompertz function. The primary generation times by this model ($k_2$) were able to compare to the other two methods, the Gompertz function gave slightly shorter generation times.

## Discussion

The postulated first-order kinetics for the A to B transition were rationalized by assuming that repair or lag time rates were limited by one step of a complex enzymatic process. The data from Foegeding and Busta (1983) indicated that spore germination was a first-order process. Another process could be postulated, however, sufficient data are not usually collected during the lag phase to permit fitting a more complex function.

**Table 4. Constants for *L. monocytogenes* growth in BHI broth with varying $a_w$.**

| Water Activity | $k_1$ ($h^{-1}$) | $k_2$ (h) | $k_3$ (log ml $cfu^{-1}$) | $k_4$ ($h^{-1}$) | Generation time (h) | |
|---|---|---|---|---|---|---|
| | | | | | Plot | Gompertz |
| 0·99 | 0·063 | 0·75 | −9·6 | 0·010 | 0·69 | 0·69 |
| 0·97 | 0·0063 | 1·0 | −9·3 | 0·0050 | 1·10 | 0·86 |
| 0·93 | 0·00063 | 2·7 | −9·3 | 0·020 | 3·20 | 2·55 |
| 0·90 | 0·050 | 7·5 | −4·0 | 0·025 | | |
| 0·87 | 0·10 | 7·0 | −4·1 | 0·036 | | |
| 0·83 | 0·10 | 6·0 | −4·3 | 0·045 | | |
| 0·80 | 0·13 | 5·0 | −4·6 | 0·12 | | |

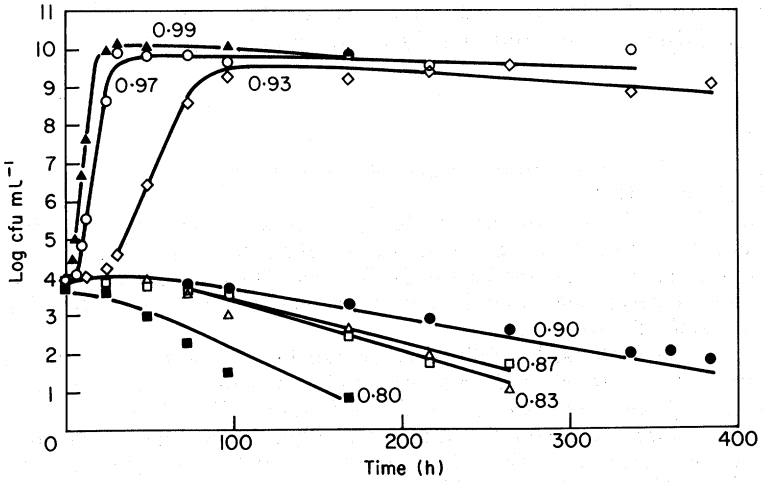


**Fig. 3.** Growth and decline of *L. monocytogenes* in BHI with varying $a_w$. Symbols represent plate count values and the lines are generated by the model using the parameter values on Table 4.

In general, short lag phases had $k_1$ values of approximately 0·1 $h^{-1}$; long lag phases had $k_1$ values of 0·001 $h^{-1}$.

The primary generation time ($k_2$) was comparable to the generation time obtained when data are plotted or fitted using the Gompertz function. Growth proceeded at this rate only in the beginning, the $k_3$ sum growth-time term immediately began to reduce the overall rate of growth. However, this limiting of growth was not usually noticeable until the negative log of the cell numbers (cfu $ml^{-1}$) approached the log value of $k_3$, typically –6 to –9. Therefore, this model has an essentially linear growth phase (log cfu $ml^{-1}$) in contrast to the continuously curving Gompertz function which may be too steep at the inflection point when the overall best fit is calculated. Values for $k_3$ were less dependent on growth parameters such as temperature or pH than the first two parameters, but presumably were related to other limiting factors in the medium.

The first-order decline parameter, $k_4$ ranged from 0·0 $h^{-1}$ to 0·3 $h^{-1}$. With curves exhibiting high death rates, this term began to exert an effect during the growth phase decreasing the apparent rate of population increase and maximum population. The inactivation of micro-organisms in water, soil and ground water was described as a first-order process (Gerba et al. 1991, Harvey 1991, Kundsen 1991).

## Conclusion

This model accurately described the shape of microbial growth curves. Its four parameters model different portions of the curve and permit quantitative comparisons of different growth conditions. Changes in the parameters may be described by multiple regression equations. The parameter changes could also be described by other relationships such as the Arrhenius or square root functions for different temperatures. The assumptions in this model invite experimental verification and subsequent modification.

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## Appendix

*Lotus spreadsheet*

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | file | RCWMODA.WK1 | BACTERIAL GROWTH MODEL | | | STD FORM | RCW-MCP | |
| 2 | | | | | | | | |
| 3 | | | log inoc | log k1 lag | k2 GT | log k3 | log k4 | time interv |
| 4 | DATA ENTRY >> | | 4 | −1 | 0·75 | −9 | −1·5 | 1 |
| 5 | | | 10000 | 0·1 | | 1·00E−09 | 0·031622 | |
| 6 | | | | | | | | |
| 7 | TIME | DATA | A | POPULATION | GROW K | SUM GROWTH LOG | CFU/ML | |
| 8 | 0 | 4 | 10000·00 | 0 | 0·75 | 0 | 4·00 | |
| 9 | 1 | | 9048·37 | 2519·8420 | 0·75 | 2519·8420 | 4·06 | Tlag 1/2 |
| 10 | 2 | | 8187·31 | 8428·8595 | 0·7500025 | 10948·701 | 4·22 | 6·9 |
| 11 | 3 | | 7408·18 | 22630·748 | 0·7500109 | 33579·449 | 4·48 | |
| 12 | 4 | | 6703·20 | 57088·569 | 0·7500335 | 90668·019 | 4·80 | |
| 13 | 5 | 5·2 | 6065·31 | 140988·37 | 0·7500906 | 231656·39 | 5·17 | |
| 14 | 6 | | 5488·12 | 345523·63 | 0·7502316 | 577180·03 | 5·55 | Tdeath 1/2 |
| 15 | 7 | | 4965·85 | 844274·11 | 0·7505771 | 1421454·1 | 5·93 | 21·8 |
| 16 | 8 | | 4493·29 | 2059948·7 | 0·7514214 | 3481402·9 | 6·31 | |
| 17 | 9 | | 4065·70 | 5018949·8 | 0·7534814 | 8500352·8 | 6·70 | |
| 18 | 10 | 7·1 | 3678·79 | 12195863 | 0·7585003 | 20696216 | 7·09 | |
| 19 | 11 | | 3328·71 | 29454108 | 0·7706962 | 50150325 | 7·47 | |
| 20 | 12 | | 3011·94 | 70111683 | 0·8001503 | 120262008 | 7·85 | |

*Spreadsheet commands*

| cell | entry |
|---|---|
| C4 | log inoculum |
| D4 | log k1 |
| E4 | k2 generation time |
| F4 | log k3 |
| G4 | log k4 |
| H4 | iteration time |
| C5 | 10^C4 |
| D5 | 10^D4 |
| F5 | 10^D4 |
| G5 | 10^G4 |

| column | entry |
|---|---|
| A | (A8+$h$4) |
| B | data |
| C | ($C$8*@EXP(–$D$5*(A9–A8)) |
| D | (($D$5*C8*(A9–A8)) + (1–$G$5*(A9–A8))*D8) *2^((A9–A8)/E8) |
| E | ($E$4+($F$5*F8*(A9–A8))) |
| F | (D9*(A9–A8))+F8 |
| G | @LOG(C9+D9) |